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(54) Title: MULTIPARTICULATE ORAL DOSAGE FORMS

(57) Abstract

A convenient oral dosage form that contains a drug that is reversibly adsorbed to an ion–exchange resin and subsequently coated with a polymeric material is provided. Compositions of the invention are particularly advantageous for formulating acid labile drug compounds and/or drug compounds that have particularly strong and unpleasant tastes or odours. Methods of manufacturing the convenient oral dosage forms and final dosage forms that include the convenient oral dosage forms are also provided.

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Description

MULTIPARTICULATE ORAL DOSAGE FORMS

Technical Field

The present invention relates to a convenient oral dosage form. In particular, the invention relates to a convenient oral dosage form containing a drug that is loaded onto an ion-exchange resin and subsequently coated.

Background Art

Oral administration represents the preferred route of administration for a wide range of pharmaceutical agents. Particular advantages associated with oral administration include ease of administration and convenience for the patient, both of which can lead to improved patient compliance. However, some drugs have an inherently bitter or unpalatable taste associated with them. This is a distinct problem if it is desirable to formulate these drugs in an oral dosage form. Various methods have been developed for masking the taste of such drugs so as to facilitate their formulation for oral administration.

US 5,032,393 (Glaxo Group Ltd.) teaches that the bitter taste of ranitidine may be masked by forming an adsorbate with a synthetic cation exchange resin. The adsorbate may then be incorporated into compositions for oral administration. Specifically, the synthetic cation exchange resin is selected from copolymers of styrene and divinylbenzene which are sulphonated, and copolymers of methacrylic acid and divinylbenzene. US 5,188,825 (Iles *et al.*) discloses a freeze-dried dosage form comprising a water-soluble active agent which is bonded to an ion-exchange resin to form a substantially water insoluble complex. The dosage form is prepared by mixing the water insoluble complex with a compatible carrier and freeze-drying the mixture. It is taught that these freeze-dried dosage forms reduce the undesirable odour

and / or taste of active agents. Chlorpheniramine maleate and phenylephrine hydrochloride compositions are given as examples.

However, it is apparent that in the case of particularly bitter or unpleasant tasting drugs the use of such drug / resin complexes or adsorbates, as described above is not sufficient to eliminate the undesirable taste. Additionally, some ion-exchange resin materials themselves have unpleasant taste characteristics which add to, rather than reduce, the problems of formulating organoleptically acceptable oral dosage forms.

Therefore, a need exists for a taste-masked composition which masks the taste of particularly bitter of unpleasant tasting drugs. It is an object of the present invention to address this need.

Further, an ion-exchange resin can be used as a vehicle onto which a drug compound may be adsorbed for release in a controlled or sustained fashion. There are a number of factors which affect the performance of such drug / resin formulations. These include choosing a suitable resin, optimising the drug load within the resin particles and ensuring that the structural integrity of the particles is maintained. The last point is of considerable importance in sustained release formulations since the drug loaded particles tend to swell in a liquid environment which can rupture any coating on the particles with the result that the drug load is dumped in an uncontrolled manner. US 4,221,778 (Pennwalt Corporation) teaches the use of an impregnating / solvating agent, which is added to the drug / resin particles prior to application of a diffusion barrier coating to retard swelling. Alternatively, US 5,186,930 (Schering Corporation) teaches the use of an inner wax coating, applied prior to enteric coating, to prevent swelling.

It has been disclosed (US 4,996,047 Richardson-Vicks Inc.) that diffusion barrier coated drug-resin particles having a critical drug load (the active ingredient making up greater than 38 % by weight of the drug-resin particles) maintain their integrity and avoid cracking. US 5,413,782 (Rhone Poulenc Rorer Pharmaceuticals) discloses a method

of achieving greater than 40 % (by weight) loading of resin particles by carrying out the loading process in the absence of carbon dioxide or bicarbonates.

Rhee et al., Yakhak Hoeji, 38(3):250-264 (1994) discloses an omeprazole-ion exchange resin complex. The particles of the complex were granulated into larger sized granules prior to coating with an enteric coating.

The documents mentioned above in relation to drug / resin formulations are based on the premise that the drug is to be delivered in a sustained or prolonged manner. The mode of action of many drugs involves reversible binding of a target molecule or receptor establishing an equilibrium between the bound state and the free target molecule or receptor and free drug. In these cases it is advantageous to have a sustained release of the active ingredient in order to ensure that the equilibrium favours the bound, and therefore therapeutically active, state. Thus, the reversible nature of the drug / target interaction in these instances dictates the use of a sustained release formulation.

One aspect of the present invention on the other hand is directed towards the delivery of drug compounds for which sustained delivery may not be of value; for example drugs, such as proton pump inhibitors, that interact in an irreversible manner with the target molecule or receptor. As such, an object of the present invention is to provide a controlled release palatable convenient dosage form for the effective delivery of such drugs including proton-pump inhibitors (hereinafter PPIs). It is another object of the present invention to provide a composition in which the active ingredient is released rapidly after an initial delay period. It is a further object of the invention to provide a stable composition for PPIs as well as other acid labile active ingredients. It is a further object of this invention to provide a preparation containing a drug / resin complex which may be used to deliver the active ingredient to a region of specific pH.

Disclosure of Invention

One aspect of the invention is a convenient oral dosage form that includes a multiparticulate composition and each particle includes an active ingredient reversibly adsorbed onto an ion exchange material to form an active ingredient-resin complex and each core is coated with a polymeric coating material. The ion exchange resin can be either a cation exchange resin or an anion exchange resin. Further, the active ingredient can be entrapped with the ion exchange material in the core. The active ingredient can be one with a strong and unpleasant taste or odour or an acid labile compound. The polymeric coating can be a pH dependent or independent polymer and can include a combination or two or more polymeric materials.

In another aspect of the invention, the oral dosage form provides taste masking for an active ingredient having a strong and unpleasant taste or odour.

In a further aspect of the invention, the oral dosage form is a controlled release dosage form such as a delayed release dosage form.

Other aspects of the invention include methods of manufacturing the oral dosage form as well as final oral dosage forms that can be either solid or liquid oral dosage forms.

Convenient oral dosage forms such as suspensions, syrups, sprinkles, fast melt tablets, effervescent tablets and fast dissolving tablets are readily acceptable to patients resulting in increased patient compliance for a given therapeutic regimen. The present invention allows for the presentation of acid labile drugs and drugs of unpleasant odour or taste into a range of different palatable convenient dosage forms. The invention is based on loading the drug, be it acid labile or unpleasant tasting, onto an ion exchange resin of opposite charge, coating the discrete resin particles with either a taste masking or enteroprotective coating and incorporating the resulting coated drug loaded resin particles into the convenient oral dosage form.

The oral dosage form of the present composition comprises a plurality of particles, each particle having a core containing an active ingredient or a pharmaceutically acceptable salt thereof and a coating material coated onto the core; wherein the core further comprises an ion exchange resin material, the active ingredient or a pharmaceutically acceptable salt thereof being reversibly adsorbed onto the ion exchange resin material to form an ion exchange resin drug complex.

The terms "active ingredient" or "drug", used interchangeably herein, includes any drug compound that is either acid labile or which is characterised by an unpleasant odour or taste and which can be bound to an ion exchange resin may be used in the present invention.

For drugs of unpleasant odour or taste the combination of complexing the drug with an ion-exchange resin and coating the resultant drug-resin complex in accordance with the invention provides good taste masking and facilitates the incorporation of the drug into dosage forms for oral administration. Complexing the drug with an ion-exchange resin prevents leaching of drug from the formulation and thus the likelihood of a bitter taste in the case of a formulation such as a fast melt tablet or liquid formulation.

Representative drugs of unpleasant taste or odour include, but are not limited to, H_2 receptor antagonists, antibiotics, analgesics, cardiovascular agents, peptides or proteins, hormones, anti-migraine agents, anti-coagulant agents, anti-emetic agents, anti-hypertensive agents, narcotic antagonists, chelating agents, anti-anginal agents, chemotherapy agents, sedatives, anti-neoplastics, prostaglandins, antidiuretic agents and the like. Typical drugs include, but are not limited to, nizatidine, cimetidine, ranitidine, famotidine, roxatidine, etinidine, lupitidine, nifentidine, niperitone, sulphotidine, tuvatidine, zaltidine, erythromycin, erythromycin derivatives such as for example ketolide (11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl(4-(4-(3-pyridinyl)-1H-imidazol-1-yl)butyl)imino)) erythromycin), penicillin, ampicillin, roxithromycin, clarithromycin,

psylium, ciprofloxacin, theophylline, nifedipine,prednisone, prednisolone, ketoprofen, acetominophen, ibuprofen, dexibufen lysinate, flurbiprofen, naproxen, codeine, morphine, sodium diclofenac, acetyl salicylic acid, caffeine, pseudoephedrine, phenylpropanolamine, diphenyhydramine, chlorpheniramine, dextrometorphan, berberine, loperamide, mefenamic acid, flufenamic acid, astemizole, terfenadine, certrizine, phenytoin, guiafenesin, N-acetylprocainamide hydrochloride, pharmaceutically acceptable salts thereof and derivatives thereof.

For acid labile drugs, the combination of complexing the drug with an ion-exchange resin and coating the resultant drug-resin complex in accordance with the invention provides protection for the drug from the acid environment of the stomach upon ingestion and facilitates the incorporation of the drug into dosage forms for oral administration. Complexing the drug with an ion-exchange resin prevents leaching of drug from the formulation in the stomach after ingestion and thus the likelihood of degradation of the drug in the case of a formulation such as a fast melt tablet or liquid formulation.

Acid labile drugs include those drug substances that are adversely affected by exposure to acidic media. Representative acid labile drugs include, but are not limited to proton pump inhibitors in general, including benzimidazole compounds, more particularly substituted 2-pyridyl methyl sulfinyl benzimidazoles, either substantially in the form of one optically pure enantiomer or, in the form of a mixture of enantiomers or racemate where applicable, and pharmaceutically acceptable salts thereof. Substituted 2-pyridyl methyl sulfinyl benzimidazoles may typically contain a chiral centre when the carbon atom of the methyl sulfinyl bridge between the benzimidazole and pyridyl moieties is bonded to four different substituent groups. Preferably the active ingredient is a substituted 2-pyridyl methyl sulfinyl benzimidazole compound. More preferably the active ingredient is selected from the group consisting of omeprazole, perprazole, lansoprazole, pantoprazole, rabeprazole and leminoprazole. Most preferably the active ingredient is omeprazole.

Acid labile active ingredients other than PPIs may also benefit from the protection afforded by the adsorption of the active onto an ion exchange material and entrapment on or within coated resin particles. An example of such an acid labile active ingredient, which is not a PPI, is erythromycin which is known to loose its antibacterial activity at pH lower than 5.5.

Ion-exchange resin materials suitable for use in accordance with the present invention include any ion-exchange resin which is capable of binding the drug, including, for instance, anionic and cationic resin materials. Where the drug is a cation or is prone to protonation, the ion-exchange resin is suitably a cation exchange resin material. That is to say, a resin having a predominantly negative charge along the resin backbone, or a resin having a pendant group suitable for cation exchange, and which has an affinity for positively charged ions or cationic species. Typical of such cation exchange resins include resins having polymer backbones comprising styrene - divinyl benzene colpolymers, methacrylic acid and divinyl benzene co-polymers, and resins with pendant functional groups suitable for cation exchange, such as sulphonate and carboxylate groups. Cation exchange resins suitable for use in the practice of the present invention include for example those sold under the trade names Amberlite IRP-64, Amberlite IRP-69 and Amberlite IRP 88 (Rohm and Haas, Frankfurt, Germany), Dowex 50WX2-400, Dowex 50WX4-400 and Dowex 50WX8-400 (The Dow Chemical Company, Midland, MI), Purolite C115HMR and Purolite C102DR (Purolite International Ltd., Hounslow, Great Britain).

Similarly, where the drug is an anion or is prone to deprotonation, the ion exchange resin is suitably an anion exchange resin material. That is to say, a resin having a predominantly positive charge along the resin backbone, or a resin having a pendant group suitable for anion exchange, and which has an affinity for negatively charged ions or anionic species. Typical of such anion exchange resins include resins having polymer backbones comprising styrene, acrylic acid or phenol units, co-polymers thereof, styrene-divinyl benzene co-polymers and phenolic-based polyamine condensates and resins with pendant

functional groups suitable for anion exchange, such as ammonium or tetraalkyl ammonium functional groups. Anion exchange resins suitable for use in the practice of the present invention include for example those sold under the trade names Amberlite IRP-58, Amberlite IRA-67, Amberlite IRA 68 (Rohm and Haas, Frankfurt, Germany), Dowex 1X2-400, Dowex 1X4-400, Dowex 1X8-400 and Dowex 2X8-400 (The Dow Chemical Company, Midland, MI), Purolite A845, Purolite A500P and Purolite PCA-433 (Purolite International Ltd., Hounslow, Great Britain), Duolite AP143/1092 and Duolite A143/1093.

Resins with various degrees of crosslinking and a range of binding capacities may also be used in the practice of the present invention.

The oral dosage forms of the present invention can be prepared by contacting the ion exchange resin with the active ingredient to form an active ingredient or drug/ ion exchange resin core or complex. The individual cores can then be coated with the polymeric coating material.

Typically the ion-exchange resins suitable for use in the present invention are in the form of ion-exchange resin particles. Stirring the ion-exchange resin particles in a solution of the selected drug is usually sufficient to achieve binding of the drug onto the resin particles. Loading of the resin is suitably carried out at a pH that facilitates binding of the drug compound. Some ion-exchange resins may require "activation" by rinsing with a solution of acid or base, prior to loading with the drug. Such activation requirements will be well known to those skilled in the art of working with ion-exchange resin materials. Specific requirements for individual ion-exchange resin materials may be obtained from the resin manufactures. Preferably, the particles are spherical to enable substantially complete coating of the particle.

The use of a suitably spherical ion exchange resin can substantially but not wholly masks the taste or odour of an active ingredient and lend itself readily to complete coating with the taste masking polymer which eliminates any residual bitter taste upon ingestion. The use of a suitably spherical ion exchange resin can help minimise the interaction of the

acid labile drug with the acidic enteroprotective coating while also facilitating the coating of the acid labile drug with the enteroprotective coating. An important aspect of the current invention is the ability to coat the drug loaded resin particles as discrete particles hence minimising the potential for a gritty aftertaste after ingestion of the drug.

The term "reversibly adsorb" means that the drug binds to an ion exchange resin of opposite charge via an ionic interaction that can be reversed in suitable ionic conditions

The active ingredient component of the composition may be present in any amount which is sufficient to elicit a therapeutic effect. Typically the active ingredient is present at about 1 - 70 % by weight of the uncoated resin. Preferably the active ingredient ranges from 5 - 60 % by weight of the uncoated resin. More preferably the active ingredient ranges from 10 - 50 %, most preferably 10-40%, by weight of the uncoated resin.

The polymer material used for coating the drug-resin complex can be a polymer that has properties which can prevent the release of the drug until it reaches a specific site in the gastrointestinal tract and only then the drug is released. The specific site in the gastrointestinal ("GI") tract includes any point in the GI tract including the oesophagus, the stomach and the intestine.

The polymer coating material used in coating the drug-resin complex may comprise a pH independent or pH dependent coating material. pH independent coating materials suitable for use in the present invention include, for example, alkyl celluloses such as methyl cellulose, hydroxyalkyl alkyl celluloses such as hydroxy propyl methyl cellulose, hydroxy alkyl celluloses such as hydroxy propyl cellulose and hydroxy ethyl cellulose, polyvinyl alcohol, maltodextrin, polymethacrylates such as Eudragit® RL (Rohm-Pharma, Darmstadt, Germany). pH dependent coating materials suitable for use in the present invention include for example esters of at least one cellulose derivative such as an alkyl cellulose, a hydroxyalkyl cellulose, a hydroxyalkyl alkyl cellulose or a

cellulose ester, with at least one polybasic acid such as succinic acid, maleic acid, phthalic acid, tetrahydrophthalic acid, hexahydrophthalic acid, trimellitic acid or pyromellitic acid. Suitable enteric coating materials include for example those selected from the group consisting of hydroxy propyl methyl cellulose phthalate (HPMCP), cellulose acetate phthalate (CAP), cellulose acetate trimillitate (CAT) and hydroxypropyl methylcellulose acetate succinate. Also considered useful in the practice of the present invention are for example enteric materials such as those selected from the group consisting of poly vinyl acetate phthalate (PVAP), polyvinyl acetaldiethylamino acetate, and shellac. Particularly useful in relation to the present invention are poly acrylic and methacrylic acids and poly acrylate and methacrylate based coatings, and mixtures thereof, such as those sold under the tradename Eudragit®, for example Eudragit L® and Eudragit S® (Rohm-Pharma, GmbH, Darmstadt, Germany) to 50 - 250 % by weight of the drug loaded resin particles. A further particularly useful pH dependent coating material suitable for use in accordance with the present invention is Eudragit® E (Rohm-Pharma, Darmstadt, Germany).

A particularly useful pH independent polymer for use in accordance with the present invention is Eudragit® RD 100 (Rohm-Pharma, Darmstadt, Germany). The polymeric coating may suitably comprise a combination of two or more polymer materials.

Acid labile drugs in the composition according to the invention are substantially protected from the enteric coated material by adsorption onto the ion exchange resin material. Thus the need for a subcoating between the active ingredient and the enteric coating is eliminated.

The coating may be applied to the drug loaded particles by any suitable technique. Such techniques will be apparent to those skilled in the art. Particularly useful for application of the coating is the technique of spray coating, carried out for instance using a fluidised bed coating apparatus. Suitable excipients and / or additives may be added to the coating formulations. For example it may be desirable to add plasticisers, glidants, anti-tacking agents, pigments and other excipients

to the coating formulations. Suitable plasticisers include, for example, triethyl citrate and polyethylene glycol. Suitable glidants include, for example, talc, syloid, glycerol monostearate and magnesium stearate. The coating material may be applied to the drug loaded particles in any amount which is sufficient to give the desired taste-masking characteristics. Typically the coating material is applied in an amount equivalent to 10 - 300 % by weight of the drug-loaded resin particles. Preferably, the coating material is applied in an amount equivalent to 20 - 250 % by weight of the drug loaded resin particles.

Without wishing to be limited by any particular theory it is believed that the physico - chemical principles underlying the present invention are as explained below. Generally speaking, acid labile benzimidazole compounds such as omeprazole are capable of binding to an anion exchange resin (i.e. a resin having a positively charged backbone). This may involve the loss of a proton leaving the benzimidazole molecule with a formal negative charge which can interact ionically with the resin. The resultant drug / resin complex particles may then be coated with an enteric coating with additional excipients if so desired. Binding of the active ingredient to the resin particles protects the drug from degradation by the acidic enteric coating. In a highly acidic environment, such as the stomach, the enteric coating protects the active ingredient from acid degradation. When the particles pass through the stomach to a region of higher pH (such as pH > 6 - 7), the enteric coating is compromised and the drug / resin complex is exposed to the surrounding environment. Exchange of negative ions, such as chloride ions, from the surrounding environment for the drug bound to the resin releases the drug, facilitating the onset of a therapeutic effect. Additionally, exposure of the drug to an even slightly acidic environment will cause it to be protonated leaving the molecule electrically neutral. These two processes would be expected to considerably reduce the drug / resin interaction, or indeed cause the drug and resin to actually repel each other. Thus the dissociation of the drug from the resin is actively promoted. Unlike the prior art drug / resin formulations in which the release of the active ingredient is sustained over a prolonged period of time, the composition of the present

invention is designed to provide a relatively rapid release of active after an initial delay. By using ion exchange resin particles as a carrier for the active ingredient, the present invention facilitates the relatively rapid delivery of active once the drug / resin particles are exposed. The enteric coating protects the drug / resin particles until they have passed through the stomach where the strongly acidic conditions would degrade the benzimidazole active ingredient. In addition, adsorption of the active ingredient on to the resin protects it from the potentially detrimental effects of the enteric coating.

Although the drug loaded resin compositions according to the present invention can be used as a final oral dosage form, they can also be adapted for a range of final oral dosage forms, including controlled release dosage forms. Suitable final dosage forms include, for example, suspension, syrup, capsule, tablet, sprinkle, sachet, effervescent tablet, fast melt tablet, fast dissolving tablet and disintegrating tablet forms. For example, the drug loaded, coated ion-exchange resin particles may be formulated in a suspension and freeze-dried to form a fast dissolving or disintegrating tablet. The compositions according to the invention may also be formulated in solid form which is reconstituted as a suspension prior to administration without losing any taste masking or entero-protective property.

Drug loaded, coated resin particles of any size suitable for incorporation into any one of the abovementioned final dosage forms may be used in the practice of the invention. Typically drug loaded, coated resin particles making up the multiparticulate composition of the present invention have an average diameter (defined as $D_{50\%}$) of 20 - 750 μm. Preferably the drug loaded, coated resin particles have an average diameter (defined as $D_{50\%}$) of 30 - 300 μm.

Conditions treatable by administration of a PPI and hence by an oral dosage form of the present include duodenal and gastric ulcers and reflux oesophagitis. A method for treating these conditions can include administering to a patient suffering from said conditions a therapeutically effective amount of a proton pump inhibitor in the form

of an oral dosage form in which the proton pump inhibitor is adsorbed onto ion exchange resin material forming cores of an ion exchange resin drug complex which are subsequently coated with an enteric coating. Specifically, the method of treatment inhibits gastric acid secretion by administering to mammals, including humans, suffering from acid secretion related conditions a therapeutically effective amount of a proton pump inhibitor in the form of an oral dosage form of the present invention.

In the following examples: all percentages are by weight (w/w) unless stated otherwise; and the term "purified water" relates to water which has been distilled and purified using an ion-exchange water purification apparatus. Omeprazole concentrations were determined using HPLC.

The invention is further illustrated by the following Examples but is not limited by these Examples.

Modes for Carrying Out the Invention

Examples

Example 1

Ketolide (11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl(4-(4-(3-pyridinyl)-1H-imidazol-1-yl)butyl)imino)) erythromycin), also referred to below as "the active ingredient" or "ketolide" composition.

In the case of the abovementioned ketolide a taste-masked powder formulation would be attractive due to the unpleasant taste characteristics of the drug. The physicochemical properties of this compound are such that as the pH of the drug in solution is lowered the drug is completely ionised, each of three nitrogen atoms being protonated according to their respective pK_a values. The protonated drug may then be loaded onto a cationic exchange resin (such as a cation

exchange resin material as listed above) to form a drug-resin complex. However, binding of this active ingredient to the ion-exchange resin is not sufficient to completely mask the taste of the drug as judged by a panel of seven. In this case coating the drug-resin complex with a coating polymer results in a composition possessing the required taste masked and organoleptic character. The formulation of a taste masked ketolide composition according to the invention is given below.

Two placebo granulates were prepared, the first having a flavouring agent added intra-granularly and the other having the flavouring agent added extra-granularly. Details of the placebo granulates are given in Table 1. The granulates were prepared as follows: the raw materials were dry mixed; purified water was added slowly until effective granulation was achieved and the granulate was left to tray-dry in an oven at *ca* 40 °C overnight. This resulting granulate was size-reduced through a 0.25 mm screen using an Erweka oscillating granulator to form a fine granulate. In the case of the intra-granular mix, the peppermint oil was added prior to the addition of water. In the case of the extra-granular mix, the peppermint oil was added to the fine granulate.

Material	"Intra-granular" (g)	"Extra-granular" (g)
Xylisorb 300	86.74	86.98
Neosorb P60	86.74	86.98
Citric acid	5.00	5.00
Aspartame	1.04	1.04
Kollidon 30	20.00	20.00
Peppermint oil	0.48	4.67

Table 1. Composition of placebo granulate with peppermint flavour added intra-granularly and extra-granularly.

The cation exchange resin (Dowex 50WX2-400, 2 Kg) was washed with purified water (5 L) for 15 min. The washed resin was recovered and loaded with the active ingredient to a potency of 400 mg drug / g drug loaded resin by mixing the resin in a solution of 8 % active ingredient in 1 N HCl for 60 min. The loaded resin was recovered by filtration, washed with purified water and oven dried at 40 °C.

The drug-resin complex was then mixed with the placebo granulate described above to form an uncoated drug-resin ketolide composition. Three different ratios of drug-resin complex to granulate were prepared using (i) the "intra-granular" and (ii) "extra-granular" placebo respectively in the following ratios: 75 : 25 (drug-resin complex : granulate); 50 : 50 (drug-resin complex : granulate); and 25 : 75 (drug-resin complex : granulate).

The uncoated drug-resin ketolide compositions thus prepared were found to have improved taste characteristics compared to the raw drug, but still had an unpleasant after taste. The taste of the resin material itself may have contributed to this.

Example 2

Taste-masked ketolide (11,12-dideoxy-3-de((2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribohexopyranosyl)oxy)-6-O-methyl-3-oxo-12,11-(oxycarbonyl(4-(4-(3-pyridinyl)-1H-imidazol-1-yl)butyl)imino)) erythromycin), also referred to below as "the active ingredient" or "ketolide" composition.

The cation exchange resin (Dowex 50WX2-400, 2 Kg) was washed with purified water (5 L) for 15 min. The washed resin was recovered and loaded with the active ingredient to a potency of 400 mg drug / g drug loaded resin by mixing the resin in a solution of 8 % the active ingredient in 1 N HCl for 60 min. The loaded resin was recovered by filtration, washed with purified water and dried in a Uniglatt (Glatt Air Techniques,) at 40 °C.

The uncoated drug-resin ketolide compositions prepared above was then coated in a Glatt GPCG1, with a 15 % aqueous solution of Eudragit RD100 : Syloid 244 FP : Polysorbate 80 (5:1:1) to a level of 50 % weight gain with Eudragit RD100, at a spray rate of 8 g / min and product temperature of 23-27 °C. The particle size of the 50 % coated resin was determined by a dry powder method in a Malvern Mastersizer S (Malvern Instruments Limited, Malvern, Worcestershire, UK) as the following: $D_{v,10}$ = 95.37μm, D_{v50} = 125.53 μm, $D_{v,90}$ = 167.85 μm. The coated drug-resin complex was found to be essentially tasteless.

Examples 3 and 4. *Omeprazole / ion exchange resin formulation using Eudragit L® coating.*

Example 3

(i) Loading of active ingredient on to resin.

Anion exchange resin PCA-433 (4,000 g) was added to a stainless steel container, washed by stirring in purified water (50 l) and subsequently activated by stirring in a solution of NaOH (1 M). The resin material particles were loaded with the active ingredient by stirring the resin in a 3.0 % solution of omeprazole (supplied by Reddy Cheminoir, Ridgewood, NJ) in NaOH (1 M) (4 l total volume of omeprazole solution) to form drug loaded particle cores. The potency of the drug solution was determined prior to and after loading on to the resin. The loaded particle cores were washed with purified water to remove any surface uncomplexed omeprazole, recovered and dried at 40 °C. After loading, the potency of the drug loaded particles cores was determined to be 177 mg/g.

(ii) Coating of drug / resin particles.

A coating solution was prepared according to the formulation shown in Table 2. The coating solution was applied to the omeprazole loaded resin particles cores using a Vector FLM-15 Fluid Bed (Vector Corp., Cranbury, NJ) coating apparatus equipped with a Wurster column. The coating solution was applied at a spray rate of 45-50 g/min, with the inlet and outlet temperatures set at 55 and 32 °C respectively and an atomisation pressure of 3 bar. The product temperature during the process was typically about 35 °C. 167 % solids with respect to the drug loaded resin particle weight was applied onto the drug loaded resin particles. Agglomeration was found to be negligible.

Component	Quantity
Eudragit® L12.5*	15,990g
Isopropanol	12,270 g
Triethylcitrate	798 g
Micronised talc	399 g

(*supplied by Rohm as a 12.5 % w/w polymer solution in isopropanol)

Table 2. Coating solution formulation for Example 3.

(iii) Acid stability and dissolution data.

The particles prepared as detailed in (i) and (ii) above, tested according to a modified version of the United States Pharmacopoeia method for enteric protection (USP 23, 1995, p. 1795). The modifications were as follows: simulated gastric fluid (0.1 M HCl/NaCl) without pepsin was used in place of 0.1 M HCl; the sample was stirred at 75 rpm (instead of 100 rpm) and filtered prior to assay. Testing for enteric protection showed no acid degradation of the omeprazole active ingredient over a period of 1 hour, indicative of good enteric protection provided by the coating. After 2 hours about 13 % of the active ingredient was found to have degraded.

The rate of release of the active ingredient under alkali conditions (pH 9.1 buffer) was determined by spectrophotometrically using an Hewlett Packard 8452A Diode Array UV spectrometer. Table 3 shows the dissolution data for the particles prepared according to the procedures detailed in (i) and (ii) (USP II paddles; 900 ml buffer pH 9.1; stirred at 100 rpm). From the data it can be seen that up to about 80 % of the active ingredient loaded on to the resin is release in under 60 mins under the test conditions.

Time (min.)	% Omeprazole released (pH 9.1 buffer)
0	0
15	48.5
30	68.5
45	74.5
60	80.3
90	85.1
120	87.4

Table 3. Dissolution data for particles prepared according to Example 3.

Example 4

(i) Loading of active ingredient on to resin.

Essentially the same procedure as detailed in Example 3 was used to prepare a second batch of omeprazole loaded resin particles. Anion exchange resin PCA-433 (4,000 g) was added to a stainless steel column, washed by passing purified water (80 l) through the column and subsequently activated using a solution of NaOH (1 M), (80 l). The resin material particles were loaded with the active ingredient by passing a 4.0 % solution of omeprazole in NaOH (1 M) through the column (40 l total volume of omeprazole solution). The potency of the drug solution

was determined spectrophotometrically prior to and after loading on to the resin. The loaded particles were washed with purified water to remove any surface uncomplexed omeprazole, recovered from the column and dried at 40 °C. After loading, the potency of the drug loaded particles cores was determined to be 370 mg/g.

(ii) Coating of drug / resin particles.

The loaded particles cores were coated using a coating solution made up in the same proportions as that detailed in Example 3 and the same coating conditions described in relation to Example 3. 200 % solids with respect to the drug loaded resin particle weight was applied onto the drug loaded resin particles. Agglomeration was found to be negligible.

(iii) Acid stability and dissolution data.

The particles prepared according to Example 4 were tested according to the USP method for enteric protection modified as described above in Example 1 and showed no acid degradation of the omeprazole active ingredient over a period of greater than 1 hour, indicative of good enteric protection provided by the coating. Further, no degradation of the active ingredient was observed after 2 hours.

The rate of release of the active ingredient under alkali conditions (pH 7.4 buffer) was determined by HPLC. Table 4 shows the dissolution data for the particles prepared according to Example 4 (USP II paddles; 900 ml buffer pH 7.4; stirred at 750 rpm). From the data it can be seen that about 93 % of the active ingredient loaded on to the resin is release in 60 mins under the test conditions.

Time (min.)	% Omeprazole released (pH 7.4 buffer)
0	0
30	77.8
45	85.7
60	93.1

Table 4. Dissolution data for particles prepared according to Example 4.

Example 5

Omeprazole / ion exchange resin formulation using HPMCP coating.

Omeprazole loaded PCA-433 resin particles were prepared substantially according to the method described in Example 3. In this instance a 1.0 % omeprazole solution (same volume) was used in loading the resin particles and the potency of the drug / loaded particles was determined to be 91 mg/g.

(ii) Coating of drug / resin particles.

A coating solution was prepared according to the formulation shown in Table 5. The coating solution was applied to the omeprazole loaded resin particles using a Glatt CPCG5 Fluid Bed (Glatt Air Techniques, Inc., Ramsey, NJ)coating apparatus equipped with a Wurster column. The coating solution was applied at a spray rate of 45-50 g/min, with the inlet and outlet temperatures set at 65 and 45 °C respectively and an atomisation pressure of 3 bar. The product temperature during the process was typically about 48 °C. 55 % solids was applied onto the

drug loaded resin particles. Some agglomeration of particles was evident.

Component	Quantity
HPMCP-HP50*	1,006 g
NH_4OH	161 g
Triethylcitrate	101 g

(*manufactured by Eastman Chemicals (Kingsport, TN))

Table 5. Coating solution formulation for Example 5.

Example 6

Preparation of fast melt tablets from Eudragit® coated omeprazole / ion exchange resin particles - blend.

(i) Manufacture of granulate.

A granulate comprising the components shown in Table 6, below, was prepared by spraying an aqueous PEG 6000 solution onto the remaining components listed in Table 6 in a Niro Aeromatic, Strea 1 granulator (Niro Aeromatic AG, Bubendorf, Switzerland) at a temperature of 27 °C and a spray rate of 10 ml/min. After spraying the material was dried for one hour in the fluidising chamber of the granulator.

Component	Quantity (g)
Sorbitol	220.4
Xylitol	220.4
Citric Acid	12.5
Aspartame	2.5
PEG 6000	25.0
Purified Water	50.0

Table 6. Granulate formulation for Example 6.

(ii) Manufacture of fast melt tablets.

The granulate prepared in (i) above was blended with omeprazole loaded enterically coated resins beads (31.25 g) prepared according to Example 3 above together with orange flavour (7.50 g) for 15 min. Magnesium stearate (1.67 g) was added and the mixture was blended for a further 5 min. Tablets were pressed using a Ronche CT 20 single station tablet press (Ronche, Milan, Italy) with a 16 mm round punch. Tablet hardness was determined using a Schleunger 6D hardness teste (Dr. Schleunger Pharmatron AG, Solothurn, Switzerland). The average tablet weight was 1249 mg with an average hardness of 8.1 kPa.

Example 7

Preparation of fast melt tablets from Eudragit® coated omeprazole / ion exchange resin particles - granulate.

Whereas the omeprazole containing resin particles were blended with a performed granulate in Example 6 above, a second batch of fast melt tablets was prepared in which the omeprazole containing resin particles were added prior to granulation. Mint flavour (7.5 g) and magnesium stearate (1.67 g) were added and the granulate, details of which are shown in Table 7, was pressed into tablets as described in the previous Example. The average tablet weight was 1190 mg with an average hardness of 5.42 kPa.

Component	Quantity (g)
Omeprazole resin particles	62.5
Sorbitol	189.6
Xylitol	189.6
Citric acid	12.5
Aspartame	2.5
PEG 6000	2.5

Table 7. Composition and weight & hardness data for fast melt tablets prepared according to Example 7.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. All patents and references described above are herein incorporated by reference.

CLAIMS: -

1. An oral dosage form comprising a multiparticulate composition, each particle comprising a core of an active ingredient reversibly adsorbed onto an ion exchange material to form an active ingredient-resin complex and each core being coated with a polymeric coating material.

2. The oral dosage form according to Claim 1, wherein the particles have an average diameter of ($D_{50\%}$) of 20-750μm.

3. The oral dosage form according to Claim 1 wherein the particles have a $D_{50\%}$ of 30-300μm.

4. The oral dosage form according to Claim 1, wherein the ion exchange resin is an anion exchange resin.

5. The oral dosage form according to Claim 1, wherein the ion exchange resin is a cation exchange resin.

6. The oral dosage form according to Claim 1, wherein the active ingredient is entrapped within the ion exchange material in the core.

7. The oral dosage form according to Claim 1, wherein the active ingredient has a strong and unpleasant taste or odour.

8. The oral dosage form according to Claim 1, wherein the active ingredient is an acid labile compound.

9. The oral dosage form according to Claim 1, wherein the active ingredient is a proton pump inhibitor compound.

10. The oral dosage form according to Claim 9, wherein the proton pump inhibitor compound is a benzimidazole compound or a pharmaceutically acceptable salt thereof.

11. The oral dosage form according to Claim 9, wherein the proton pump inhibitor compound is selected from lansoprazole, leiminoprazole, omeprazole, pantoprazole, perprazole and rabeprazole or a pharamaceutically acceptalbe salt thereof.

12. The oral dosage form according to Claim 1, wherein a polymeric coating material is effective to release the active ingredient at a specific site in the gastrointestinal tract following oral administration.

13. The oral dosage form according to Claim 12, wherein the specific site in the gastrointestinal tract is selected from the group consisting of the oesophagus, the stomach and the intestine.

14. The oral dosage form according to Claim 1, wherein the polymeric coating material is a pH dependent polymer.

15. The oral dosage form according to Claim 1, wherein the polymeric coating material is a pH independent polymer.

16. The oral dosage form according to Claim 1, wherein the polymeric coating material comprises a combination of two or more polymeric materials.

17. The oral dosage form according to Claim 1, wherein the active ingredient is a ketolide antibiotic.

18. The oral dosage form according to Claim 1, wherein the active ingredient is erythromycin.

19. A method of manufacturing the oral dosage form according to Claim 1, which comprises steps of:

(a) contacting an ion exchange resin material with the active ingredient to form an ion-exchange resin drug complex core; and

(b) coating the individual cores with the polymeric coating material.

20. A final oral dosage form comprising the oral dosage form according to Claim 1, wherein the final oral dosage form is selected from the group consisting of a liquid oral dosage form and a solid oral dosage form

21. The final oral dosage form according to Claim 20, wherein the solid oral dosage form is selected from the group consisting of a capsule, a tablet, a sprinkle, a sachet, an effervescent tablet, a fast melt tablet, a fast dissolving tablet and disintegrating tablet forms.

22. The final oral dosage form according to Claim 20, wherein the solid oral dosage form may be reconstituted as a suspension prior to administration.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/IE 00/00003

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/50 A61K47/48 A61K31/4439 A61K31/7048

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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A	FR 2 134 503 A (SASUCO) 8 December 1972 (1972-12-08) claims 1,5,10	1-3,5-8, 12-14, 18-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 May 2000	18/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Benz, K

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INTERNATIONAL SEARCH REPORT

Inte. onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	CHEMICAL ABSTRACTS, vol. 121, no. 20, 14 November 1994 (1994-11-14) Columbus, Ohio, US; abstract no. 238249, G.J. RHEE ET AL.: "development of a new omeprazole-ion exchange complex" XP002086373 abstract & YAKHAK HOECHI, vol. 38, no. 3, 1994, pages 250-264, S. Korea cited in the application	1-4,6, 8-14

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